

REMARKS

The Office Action mailed December 19, 2003 has been carefully reviewed and the foregoing amendments are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application.

Invention Disclosure Statements

The Examiner indicates that only the 1449 form filed on November 6, 2002 can be found. Applicants filed 1449 forms on November 27, 2002, October 30, 2002, July 3, 2002 and November 19, 2001. Copies of each of these 1449 forms and associated documentation are included herewith.

Objection to the Claims

In paragraph 4 the Examiner objects to claims 20, 25, 29 and 33. Applicants have amended these claims as suggested by the examiner.

In paragraph 5 the Examiner objects to claims 20, 25 and 29 and suggests the following change: "to be present on fragments that were cut on one end by the first restriction enzyme and on the other end by the second restriction enzyme are enriched in the amplification product relative to the fragments that were" should be "to be presented present on the fragments that ~~were~~ are cut on one end by the first restriction enzyme and on the other end by the second restriction enzyme are enriched in the amplification product relative to the fragments that ~~were~~ are". Applicants have made each of the suggested changes except for the substitution of "presented" for "present". It is not clear to Applicants why this suggestion was made. Some fragments contain polymorphisms and some do not, Applicant's array is designed to detect the polymorphisms that are contained in, or present on, the subset of fragments that are flanked by recognition sites for the first and the second restriction enzymes. Present here is used to indicate that a given polymorphism is located within a fragment.

In paragraph 6 the Examiner objects to claim 24 and suggests that "were" should be changed to "are". Applicants have made the suggested change.

In paragraph 7 the Examiner objects to claims 25 and 29 and suggests that "polymorphisms" be changed to "polymorphism". Applicants respectfully disagree. In claims 25 and 29 "polymorphisms" is used in the context of describing an array of probes to detect a plurality of polymorphisms. The polymorphism of the preamble is the polymorphism to be genotyped but it is only one of the polymorphisms that the array is designed to genotype. To clarify this applicants have amended claims 25 and 29 to indicate that the array is designed to genotype "a plurality of polymorphisms".

In paragraph 8 the Examiner objects to claims 29 and 33 and suggests that "fragmenting the nucleic acid sample" should be "fragmenting the first nucleic acid sample". Applicants have made the suggested change.

Rejection under 35 USC § 112, second paragraph

In paragraph 11, claims 20, 25, 29, and 33 have been rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. These claims have been amended herein to clarify that the desired fragments, those cut on one end by a first restriction enzyme and on the other end by a second restriction enzyme, are enriched during amplification relative to the fragments that have been cut on both ends by either the first restriction enzyme and ligated to only the first adaptor or by the second restriction enzyme and ligated only to the second adaptor. Support for this clarification may be found in Figure 1.

In paragraphs 12 and 13, claims 20, 25, and 29 have been rejected as being vague and indefinite in view of the phrase "the alleles present at polymorphisms". The Examiner suggests that an allele cannot be present at a polymorphism because an allele is broader than a polymorphism. Applicant's respectfully disagree with the Examiner's assertion that allele must be broader than a polymorphism. An allele is an alternative form of a locus so it may encompass a single polymorphism and Applicants have used the term allele to encompass an alternative form of a polymorphism. However, in the interest of facilitating the issuance of the claims Applicants have amended the claims to change "allele" to "sequence". Support for this clarification may be found on page 12, lines 8-10, and on page 13, lines 8-10.

In paragraph 14, claim 33 has been rejected as being vague and indefinite in view of the phrase "the presence or absence of one or more alleles of one or more polymorphisms". Again, the Examiner suggests that an allele cannot be present at a polymorphism because an allele is

broad than a polymorphism. Applicants again respectfully disagree with the assertion that an allele must be broader than a polymorphism. In the interest of facilitating the issuance of the claims Applicants have amended the claims so that it reads "determining the sequences present at one or more polymorphisms". Applicants believe that this amendment addresses the Examiner's concerns.

In paragraph 15, claims 35-39 have been rejected because the phrase "the first nucleic acid sample" lacks sufficient antecedent basis. Applicants have amended the claim as suggested by the Examiner.

In paragraph 16, claim 41 has been rejected because the limitation "each adaptor" lacks sufficient antecedent basis. Claim 41 is canceled herein making this rejection moot.

Rejection under 35 USC § 102(e) – McCasky Feazel et al.

In paragraph 18, the Examiner rejected claims 20, 24-27, 33, and 40 under 35 USC § 102(e) as being anticipated by McCasky Feazel *et al.* (U.S. Patent No. 6,100,030).

The Examiner indicates that McCasky Feazel *et al.* discloses enriched amplification of fragments that are cut on one end by a first restriction enzyme and on the other end by the second restriction enzyme. Applicants respectfully disagree. The products of the digestion with Mse I and Eco RI would be some fragments that are cut on both ends with Mse I, some that are cut on both ends with Eco RI and some that are cut on one end with Mse I and on the other end with EcoRI. The Eco RI adaptor ligates to the fragments cut with EcoRI and the MseI adaptor ligates to the fragments cut with EcoRI. The amplification is with a first primer that is complementary to the EcoRI adaptor and a second primer that is complementary to the MseI adaptor. During the amplification the fragments that are cut on both ends by the same restriction enzyme will be amplified with the same efficiency as the fragments that are cut on one end by the first enzyme and on the other end by the second enzyme. McCasky Feazel *et al.* do not teach a mechanism to preferentially amplify only those fragments that are cut on one end by the first enzyme and on the other end by the second enzyme as claimed in the amended claims.

Claims 20, 25, 29, and 33 have been amended herein to clarify that during the amplification process the fragments that have been cut by a first enzyme on one end and by a second enzyme on the other end are preferentially amplified relative to the fragments that have been cut on both ends by the same enzyme, resulting in enriched amplification of the subset of

fragments that have been cut on one end by a first enzyme and on the other end by a second enzyme. The claims have been further amended to clarify that the adaptors are designed to block ligation of one strand of the adaptor to the fragments so that fragments that have the same adaptor ligated to both ends are not amplified efficiently because there is no complete template strand. Support for these amendments is found on page 16, lines 6-9, and 29-30. Applicants believe that these amendments clarify differences between the present claims and the methods taught by McCasky Feazel. Applicants respectfully request withdrawal of the rejection.

Claims 24, 26, 27, and 40 have also been rejected as being anticipated in view of McCasky Feazel. All of these claims are dependent upon claims 20 and 25. In view of the amendments made to claims 20 and 25 and the arguments above Applicants respectfully request withdrawal of the rejection.

Rejection under 35 USC § 103(a) – McCasky Feazel in view of Guire et al.

In paragraph 20 claims 29-31 are rejected under 35 USC § 103(a) over McCasky Feazel et al. as applied to claims 20, 24-27, 33, and 40, in further view of Guire et al. (U.S. Patent No. 6,514,768).

As indicated above, McCasky Feazel et al. fail to teach a method to preferentially amplify only those fragments that are cut on one end by the first enzyme and on the other end by the second enzyme as claimed in amended claims 20, 25, 29 and 33. Guire et al. also fail to teach a mechanism to preferentially amplify only those fragments that are cut on one end by the first enzyme and on the other end by the second enzyme. Therefore, Guire et al. fails to remedy the deficiencies of McCaskey Feazel et al.

Rejection under 35 USC § 103(a) – McCasky Feazel in view of Makarov et al.

In paragraph 21 claim 41 is rejected under 35 USC § 103(a) over McCasky Feazel et al. as applied to claims 20, 24, 25, 29, and 40, in further view of Makarov et al. (U.S. Patent No. 6,197,557).

As indicated above, McCasky Feazel et al. fail to teach a method to preferentially amplify only those fragments that are cut on one end by the first enzyme and on the other end by the second enzyme as claimed in amended claims 20, 25, 29 and 33. Makarov et al. also fail to teach a mechanism to preferentially amplify only those fragments that are cut on one end by the first

enzyme and on the other end by the second enzyme. Therefore, Makarov *et al.* fails to remedy the deficiencies of McCaskey Feazel *et al.*

Rejection under 35 USC § 103(a) – McCaskey Feazel in view of Makarov et al. and Su et al.

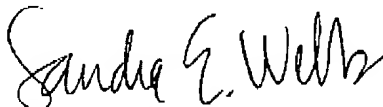
In paragraph 22 claims 41, 42, and 46 are rejected under 35 USC § 103(a) as unpatentable over McCaskey Feazel, as applied to claims 20, 24, 25, 29, and 40, in further view of Su *et al.* (U.S. Patent No. 6,632,611). Applicants believe that the Su *et al.* reference should not preclude patentability of the present application according to 35 U.S.C. 103(c), because at the time the invention claimed in 09/920,491 was made, the subject matter of the Su *et al.* patent, U.S. Patent No. 6,632,611, and the invention claimed in 09/920,491 were subject to an obligation of assignment to Affymetrix, Inc. The inventors of Su *et al.* are Shoulian Dong and Xing Su and the inventor of the invention claimed in 09/920,491 is Shoulian Dong. Xing Su and Shoulian Dong were employees of Affymetrix at the time of both inventions and had both executed employment agreements obligating them to assign to Affymetrix all inventions made as a result of their employment by Affymetrix.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe all pending claims are now in condition for allowance and should be passed to issue. If the Examiner feels that a telephonic interview would in any way expedite the prosecution and allowance of this application, please do not hesitate to call the undersigned at (408) 731-5768. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

Dated: March 19, 2004

Respectfully submitted,



Sandra E. Wells
Reg. No. 52,349

Affymetrix, Inc.
3380 Central Expressway
Santa Clara, CA 95051
Tel: 408-731-5000
Fax: 408-731-5392